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09/424,840	12/03/1999	PETER BERCHTOLD	P564-9049	8688

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EXAMINER	
HELMS, LARRY RONALD	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/424,840	Applicant(s) BERCHTOLD ET AL.	
	Examiner Larry R. Helms	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 February 2002 and 09 November 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) *1-12,17,18,20-25,28 and 29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-16,19,26 and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

El ction/Restrictions

1. Applicant's election without traverse of Group II, claims 13-16, 19, 26-27 in Paper No. 14 is acknowledged.

2. Claims 1-12, 17-18, 20-25, 28-29 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 14.

3. Claims 13-16, 19, 26-27 are under examination.

Specification

4. The disclosure is objected to because of the following informalities:

a. The first line of the specification should indicate this application is the national phase of PCT/EP98/03397 filed 06/05/98..

b. The use of the trademark ReoPro on page 14, line 20 has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Appropriate correction is required.

Claim Objections

5. Claims 13-16, 19, 26-27 are objected to because of the following informalities:

a. The claims need to recite the SEQ ID NO which corresponds to the sequence in claims 13 and 26. Although a proper search can be performed based on the insertion of the SEQ ID Nos into the specification, the claims need to have the SEQ ID Nos added.

Appropriate correction is required.

Claim Rejections - 35 USC § 101

6. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

7. Claims 13-15, 26 are rejected under 35 U.S.C. § 101 because the claimed invention is directed to non-statutory subject matter.

Claims 13-15, and 26, as written, do not sufficiently distinguish over antibodies as they exists naturally because the claims do not particularly point out any non-naturally occurring differences between the claimed antibodies and binding compositions and the structure of naturally occurring antibodies. It is well known that in autoimmune diseases, antibodies against self-antigens are

generated and the claims as currently recited encompass these naturally-occurring compositions.

In the absence of the hand of man, the naturally occurring antibodies are considered non-statutory subject matter (Diamond v. Chakrabarty, 206 U.S.P.Q. 193 (1980)). It should be noted that the mere purity of a naturally occurring product does not necessarily impart patentability (Ex parte Siddiqui, 156 U.S.P.Q. 426 (1966)). However, when purification results in a new utility, patentability is considered (Merck Co. v. Chase Chemical Co., 273 F.Supp 68 (1967), 155 USPQ 139, (District Court, New Jersey, 1967)). Amendment of the claims to recite "an isolated or purified" antibody or similar language would obviate this rejection.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 26-27 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 26-27 have been added in the amendment filed 8/16/01. Claim 26 recites the limitation of "a nucleotide sequence which encodes an amino acid sequence having...., with the proviso that when the nucleic acid encompasses a nucleotide

sequence according to (b), it does not simultaneously comprise the nucleotide sequence which encodes the amino acid sequences SGSSSNIGSNTVN and SNNQRPS, and....it does not simultaneously comprise ....." in part (c). The response filed 8/16/01 states that support for claim 26 can be found on page 12 of the present Specification. Page 12 does not contain the recited limitations or support for the negative proviso limitation or the sequences listed. Applicant is requested to provide specific support for the limitations in the specification as originally filed or remove them from the claim.

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 13-16, 19, 26-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 13-16, 19, 26-27 are indefinite for reciting "derivative" in claim 13 and 26 because the exact meaning of the term is not clear. The term "derivative" is not one which has a universally accepted meaning in the art nor is it one which has been adequately defined in the specification. The primary deficiency in the use of this phrase is the absence of a ascertainable meaning for said phrase. Since it is unclear how the heavy chain of the antibodies are to be derivatized to yield the class of derivatives referred to in the claims, there is no way for a person of skill in the art to ascribe a discrete and identifiable class of compounds to said phrase. Further, it is not clear whether the "derivative" of the

human antibody is formed by attachment of a detectable marker, therapeutic molecule, some other molecule or altering the amino acid sequence of the heavy chain, for examples. In addition, since the term "derivative" does not appear to be clearly defined in the specification, and the term can encompass proteins with amino acid substitutions, insertions, or deletions, antibody fragments, chemically derivatized molecules, or even antibody mimetics. In absence of a single defined art recognized meaning for the phrase and lacking a definition of the term in the specification, one of skill in the art could not determine the metes and bounds of the claims.

b. Claims 26-27 are indefinite for reciting part (c) in claim 26. Claim 26 recites the phrase "it does not simultaneously" this phrase is indefinite because it is not clear what the term "it" refers to. Does the term "it" refer to the nucleic acid of part c or to part b? In addition, the phrase "when the nucleic acid comprises a nucleotide sequence according to (c), it does not simultaneously comprise nucleotide sequences which encode the amino acid sequences SGSSSNIGSNTVN" is not clear because part (c) already does not encode the sequence SGSSSNIGSNTVN. Does the phrase mean that additionally it does not encode for RNNQRPS? In addition, it is not clear if the recited sequences are in the light chain or the heavy chain in a CDR, or framework regions.

c. Claims 14 and 15 are indefinite for reciting "comprises the variable domain of the H chain and/or the variable domain of the L chain" in claim 14. The phrase is not clear since claim 13 recites a heavy chain and the heavy chain comprises a variable domain. Does the phrase mean that the polypeptide that

comprises a CDR3 of claim 13 further comprises the variable domain of the heavy chain and the variable domain of the light chain or does the polypeptide comprise CDR3 of the heavy chain and a L chain variable domain? Likewise claim 15 is indefinite because it is not clear what the polypeptide in claim 14 is claiming.

d. Claim 16 is indefinite for reciting "coupled to a labeling group" because the exact meaning of the phrase is not clear. Does the phrase mean a chemical moiety that a label can be conjugated to or does the phrase mean a label such as a radiolabel or detectable label?

e. Claims 13-16, 19, 26-27 are indefinite for reciting "comprises a CDR3 region" in claims 13 and 26 because the exact meaning of the phrase is not clear. Is the CDR3 region in claim 13 for the heavy chain or the light chain and is the CDR3 region in claim 26 for the light chain or the heavy chain?

f. Claims 19 and 27 are indefinite for reciting "the active component...together with other active components" because the exact meaning of the phrase is not clear. If the polypeptide is the active component then what is contemplated to be "other active components"?

12. Claims 13-16, 19, 26-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polypeptide which comprises a heavy chain and a light chain of a human antibody wherein the antibody binds GPIIb/IIIa and antigen binding fragments thereof wherein the

antibody or fragments are labeled and compositions comprising such, does not reasonably provide enablement for any polypeptide that encodes a heavy chain which binds GPIIb/IIIa which comprises a CDR3 region of SEQ ID NO:31 or 32 or an amino acid sequence that is at least 80% to SEQ ID NO:31 or 32, or a polypeptide that further comprises any light chain with a CDR3 of SEQ ID NO:37 or 38 or a polypeptide that is 80% homology to SEQ ID NO:37 or 38 or does not have the sequences recited in claim 26 (c) and pharmaceutical compositions comprising such. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims encompass polypeptides of a heavy chain that binds to GPIIb/IIIa that has a CDR3 region of a specific sequence or 80% identical to those sequences and fragments thereof and further comprises any light chain or any light chain that has a CDR3 region of a specific sequence or a sequence that is 80% identical to those sequences but does not contain certain other

sequences and fragments thereof. The specification teaches antibodies which comprise a specific heavy chain and a specific light chain that pair to bind to GPIIb/IIIa (see Table 3, 7a and b). The specification does not enable a heavy chain that alone binds GPIIb/IIIa that only comprises a CDR3 region of SEQ ID NO:31 or 32 or 80% identical to SEQ ID NO:31 or 32, or a polypeptide that comprises such and further comprises just any light chain or a light chain that only comprises a CDR3 region of SEQ ID NO:37 or 38 or 80% identical with the proviso that it does not comprise sequences recited in claim 26 (c).

The claims are not commensurate in scope with the enablement provided in the specification. It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as

evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that polypeptides as defined by the claims which may contain less than the full complement of CDRs from the heavy and light chain variable regions of an antibody in unspecified order, have the required binding function. The specification provides no direction or guidance regarding how to produce polypeptides as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone. Further, In at least one case it is well known that an amino acid residue in the framework region is involved in antigen binding (Amit et al Science Vol 233 747-753 1986) and thus, just having a CDR3 region or a specific CDR3 region is not enough structure for antigen binding.

Further, a fragment of the heavy chain can be any one of the constant regions (CH1-3) and also may be the hinge region. However, the language also reads on small amino acid sequences which are incomplete regions of the constant region of the polypeptide. One of skill in the art would neither expect nor predict the appropriate functioning of the polypeptide as broadly as is claimed.

Claims 19 and 27 are drawn to a pharmaceutical compositions comprising an effective amount of the polypeptide which comprises a specific CDR3 region. Enablement of a "pharmaceutical composition" is considered to rest on a teaching of in vivo administration for purposes consistent with the intended use

disclosed in the specification. The disclosed intended use for the claimed pharmaceutical compositions/vaccine is for the production of antiidiotypic antibodies for therapy of AITP (see page 13, lines 23-35). Thus, the nature of the invention is an immunogenic/therapeutic composition used in the treatment AITP.

Although the specification discloses the claimed composition, and general methods for formulating compositions in pharmaceutically acceptable carriers, there is insufficient guidance which would enable one skilled in the art to use the claimed compositions for their intended purpose, viz., for the generation of a protective immune response.

At the time the invention was made, pharmaceutical compositions/vaccines comprising the claimed polypeptides were not routinely used for the treatment of AITP. The specification lacks guidance by way of general methods or working examples which teach that only the CDR3 region is necessary for antiidiotypic antibody response. Lack of working examples is given added weight in cases involving an unpredictable and undeveloped art, such as immunotherapy of AITP. In addition, it is well known that a polypeptide can have many conformations in solution and it is critical that for antiidiotypic antibodies to mimic the antigen that a proper conformation be obtained. This is underscored by Chatterjee et al (U.S. Patent 6,274,143, filed 6/98) which teach antibodies (Ab1) to the antigen bind to the antigen and antibodies to Ab1, Ab2, can mimic the antigen (see column 2, lines 10-20). Thus, the entire antibody in its proper three dimensional structure is needed to illicit anti-ids.

Therefore, in view of the lack of predictability in the art as evidenced by Rudikoff et al, Amit et al, and Chatterjee et al and the lack of guidance in the specification one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention.

Claim Rejections - 35 USC § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 13-16, 19, 26-27 are rejected under 35 U.S.C. 102(b) as being anticipated by Berchtold (Blood 74:2414-2417, 1989).

The claims recite a polypeptide which is encoded by a nucleic acid which encodes a heavy chain which is able to bind to GPIIb/IIIa and comprises a CDR3 region which is SEQ ID NO:31, 32, or 80% identical to SEQ ID NO:31 or 32 and which is coupled to a labeling group and further comprises a light chain and the light chain comprises a CDR3 region of SEQ ID NO:37, 38, or 80% identical to SEQ ID NO:37 or 38 and compositions comprising such. For this rejection the art is applied to what is enabled and the intended use of a pharmaceutical composition is given no patentable weight. In addition, because of the indefinite

nature of claim 26 (c) it is interpreted to be a sequence that is 80% homology to SEQ ID NO:37 or 38. Claim 16 is interpreted to be coupled to a label.

Berchtold et al teach autoantibodies to GPIIb/IIIa from patients with ITP and compositions comprising such with PBS and the antibodies were labeled with biotin (see page 2414 and 2415). It would be inherent that the amino acids of the polypeptides of Berchtold et al are encoded by a nucleic acid.

Berchtold et al is silent as to the amino acid sequence of the antibodies, however, it is the Examiner's position that Berchtold et al have produced antibodies which are directed to the same antigen and isolated from the same patients as the claimed antibodies. One of ordinary skill in the art would reasonably envisage that Berchtold et al's antibody also possesses the same structural and functional properties as those of the antibodies claimed and, therefore, it appears that Berchtold et al have isolated antibodies that are identical to the claimed antibody. Since the Patent and Trademark Office does not have the facilities for examining and comparing the claimed polypeptides with the antibody of Berchtold et al, the burden of proof is upon the Applicants to show a distinction between the structural and functional characteristics of the claimed polypeptides and antibody of the prior art. See In re Best, 562 F.2d 1252, 195 U.S.P.Q. 430 (CCPA 197) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

15. Claims 13-16, 19, 26-27 are rejected under 35 U.S.C. 102(b) as being anticipated by Nugent et al (Blood 70:16-22, 1987).

The claims have been described supra. For this rejection the art is applied to what is enabled and the intended use of a pharmaceutical composition is given no patentable weight. In addition, because of the indefinite nature of claim 26 (c) it is interpreted to be a sequence that is 80% homology to SEQ ID NO:37 or 38. Claim 16 is interpreted to be coupled to a label.

Nugent et al teach autoantibody 5E5 which binds to GPIIb/IIIa from a patient with ITP and compositions comprising such and the antibodies were labeled with I125 (see page 16-17). It would be inherent that the amino acids of the polypeptides of Nugent et al are encoded by a nucleic acid.

Nugent et al is silent as to the amino acid sequence of the antibodies, however, it is the Examiner's position that Nugent et al have produced antibodies which are directed to the same antigen and isolated from the same patients as the claimed antibodies. One of ordinary skill in the art would reasonably envisage that Nugent et al's antibody also possesses the same structural and functional properties as those of the antibodies claimed and, therefore, it appears that Nugent et al have isolated antibodies that are identical to the claimed antibody. Since the Patent and Trademark Office does not have the facilities for examining and comparing the claimed polypeptides with the antibody of Nugent et al, the burden of proof is upon the Applicants to show a distinction between the structural and functional characteristics of the claimed polypeptides and antibody of the prior art. See In re Best, 562 F.2d 1252, 195 U.S.P.Q. 430 (CCPA 197) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

Conclusion

16. No claim is allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

18. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4242.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879